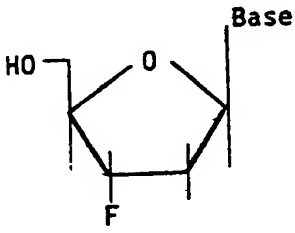




INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification⁴ : A61K 31/70, C07H 19/04, 19/06 C07H 19/16	A1	(11) International Publication Number: WO 88/ 00050 (43) International Publication Date: 14 January 1988 (14.01.88)
(21) International Application Number: PCT/SE87/00316 (22) International Filing Date: 2 July 1987 (02.07.87) (31) Priority Application Number: 8602981-6 (32) Priority Date: 4 July 1986 (04.07.86) (33) Priority Country: SE (71) Applicant (for all designated States except US): ASTRA LÄKEMEDEL AKTIEBOLAG [SE/SE]; S-151 85 Södertälje (SE). (72) Inventors; and (75) Inventors/Applicants (for US only) : ERIKSSON, Bertil, Frank, Harald [SE/SE]; Lindhovsvägen 35, S-147 00 Tumba (SE). JOHANSSON, Karl, Nils, Gunnar [SE/SE]; Bäverstigen 19, S-150 23 Enhörna (SE). STENING, Göran, Bertil [SE/SE]; Vårbovägen 10, S-151 50 Södertälje (SE). ÖBERG, Bo, Fredrik [SE/SE]; Askvägen 27, S-752 52 Uppsala (SE).		(74) Agents: MIKSCHKE, Gerhard et al.; AB Astra, Patent and Trademark Department, S-151 85 Södertälje (SE). (81) Designated States: AT (European patent), AU, BE (European patent), CH (European patent), DE (European patent), DK, FL, FR (European patent), GB (European patent), IT (European patent), JP, LU (European patent), NL (European patent), NO, SE (European patent), US. Published <i>With international search report.</i>
(54) Title: NOVEL MEDICINAL USE OF NUCLEOSIDES <div style="text-align: center;">  <p style="text-align: right;">(I)</p> </div> (57) Abstract <p>Use of a compound of formula (I), wherein Base is thymine, cytosine, adenine or guanine, or a physiologically acceptable salt thereof, for manufacture of a medicament for therapeutic or prophylactic control or treatment of retrovirus infections, including HIV, or hepatitis B virus infections. A method for such control or treatment, especially for AIDS, is also disclosed.</p>		

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	FR	France	ML	Mali
AU	Australia	GA	Gabon	MR	Mauritania
BB	Barbados	GB	United Kingdom	MW	Malawi
BE	Belgium	HU	Hungary	NL	Netherlands
BG	Bulgaria	IT	Italy	NO	Norway
BJ	Benin	JP	Japan	RO	Romania
BR	Brazil	KP	Democratic People's Republic of Korea	SD	Sudan
CF	Central African Republic	KR	Republic of Korea	SE	Sweden
CG	Congo	LI	Liechtenstein	SN	Senegal
CH	Switzerland	LK	Sri Lanka	SU	Soviet Union
CM	Cameroon	LU	Luxembourg	TD	Chad
DE	Germany, Federal Republic of	MC	Monaco	TG	Togo
DK	Denmark	MG	Madagascar	US	United States of America
FI	Finland				

Novel medicinal use of nucleosides.

Field of the Invention

The present invention relates to the use of known chemical compounds and physiologically acceptable salts thereof for the therapeutic and
5 prophylactic control and treatment of the Acquired Immuno Deficiency Syndrome (AIDS), infections by Human Immunodeficiency Virus, hepatitis B virus infections and retrovirus infections for such control and treatment in animals and man.

10 Background of the Invention

In the late seventies a new disease was reported, which subsequently was referred to as Acquired Immuno Deficiency Syndrome (AIDS). It is now generally accepted that a retrovirus referred to as HIV (Human Immuno
15 Deficiency Virus, formerly known as Human T-cell Lymphotropic Virus (HTLV-III) or Lymphadenopathy Associated Virus (LAV) plays an essential role in the etiology of AIDS.

AIDS is characterized by a profound immunodeficiency due to low numbers
20 of lymphocyte-T-helper cells, which are the targets for HIV (also called HTLV-III/LAV) infection. The profound immunodeficiency in AIDS patients makes these patients highly susceptible to a variety of opportunistic infections of bacterial, fungal, protozoal or viral etiology. The etiological agents among viral opportunistic infections are often found
25 in the herpes virus group, i.e., Herpes simplex virus (HSV), Varicella Zoster virus (VZV), Epstein-Barr virus (EBV) and, especially, cytomegalovirus (CMV). Other retroviruses affecting humans are HTLV-I and II and examples of retroviruses affecting animals are feline leukemia virus and equine infectious anaemia virus.

30 Hepatitis B virus infections cause severe disease such as acute hepatitis, chronic hepatitis, fulminant hepatitis in a considerable number of persons. It is estimated that there are 200 million patients

with chronic hepatitis B infection in the world. A considerable number of the chronic cases progress to liver cirrosis and liver tumours. In some cases the hepatitis infections also take a rapid and severe course as in fulminant B hepatitis with about 90 % mortality. At present there is no known effective treatment against hepatitis B infections.

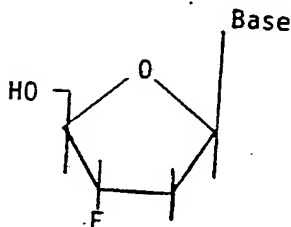
Prior Art

The compounds 3'-deoxy-3'-fluoro-thymidine and 2',3'-dideoxy-3'-fluoro-cytidine are described in Journal f. prakt. Chemie. Vol. 315, 895-900 (1973) as agents having cytostatic and virostatic activity as selective inhibitors of DNA synthesis.

The compounds 2',3'-dideoxy-3'-fluoroadenosine and 2',3'-dideoxy-3'-fluoroguanosine are described in the East-German patents DD 158903 and DD 209197, respectively, as virostatic agents.

Disclosure of the Invention

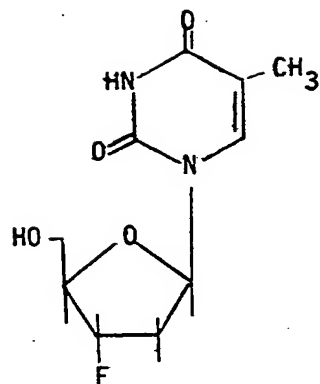
It has been found according to the present invention that the compounds of the formula



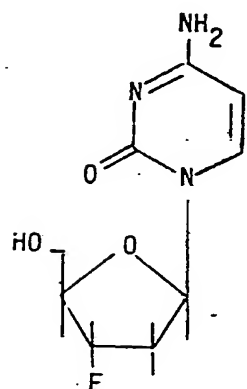
wherein Base is thymine, cytosine, adenine or guanine, or a physiologically acceptable salt thereof, present a new possibility to block the multiplication of retrovirus, including HIV, and hepatitis B virus, respectively, by use a nucleoside analogue of said formula. Accordingly, the nucleoside analogues of said formula and physiologically acceptable salts thereof, have unobvious and beneficial properties as prophylactic and/or therapeutic agents in the control or treatment of retrovirus and hepatitis B virus infections, respectively. Said nucleosides are especially interesting as agent capable of inhibiting the activity of human immunodeficiency virus (HIV; HTLV-III/LAV virus) in animals and man.

All retrovirus, including (HIV, HTLV-III/LAV), require an enzyme called reverse transcriptase in their natural cycle of replication.

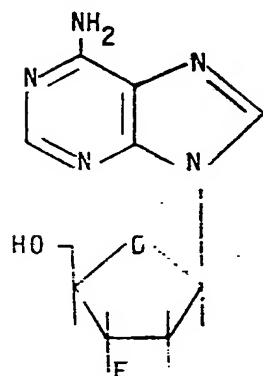
- 5 Hepatitis B virus (HBV) is a DNA virus with a unique circular double-stranded DNA genome which is partly single-stranded. It contains a specific DNA polymerase required for viral replication. This DNA polymerase also acts as a reverse transcriptase during the replication of HBV DNA via an RNA intermediate.
- 10 The compounds of the invention are transformed by cells/or enzymes to triphosphates which inhibit the reverse transcriptase of retrovirus including HIV as well as the activity of DNA polymerase of hepatitis B virus.
- 15 The following known compounds constitute part of the invention as prophylactic and therapeutic agents in control or treatment of retrovirus or hepatitis B virus infections:
-



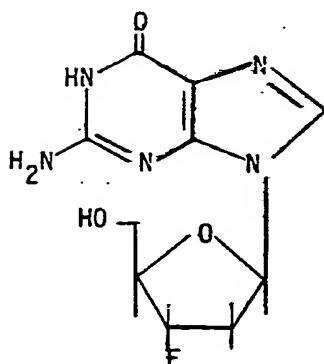
3'-deoxy-3'-fluorothymidine



2',3'-dideoxy-3'-fluorocytidine



2',3'-dideoxy-3'-fluoroadenosine



2',3'-dideoxy-3'-fluoroguanosine

3'-Deoxy-3'-fluorothymidine is especially preferred as an agent for use in control or treatment of retrovirus, including HIV (HTLV-III/LAV) and hepatitis B virus infections in animal and man.

- 5 In clinical practice the nucleosides of the invention will normally be administered orally, by injection or by infusion in the form of a pharmaceutical preparation comprising the active ingredient in the form of the original compound or optionally in the form of a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable carrier which may be a solid, semi-solid or liquid diluent or an ingestible capsule. The compound may also be used without carrier material. As examples of pharmaceutical preparations may be mentioned tablets, dragées, capsules, granulates, suspensions, elixirs, syrups, solutions etc. Usually the active substance will comprise between 0.05 and 20 % for preparations intended for injection and between 10 and 90 % for preparations intended for oral administration.

- In the treatment of patients suffering from retrovirus especially HIV or hepatitis B virus infections, it will be preferred to administer the compounds by any suitable route including the oral, parenteral, rectal, nasal, topical and vaginal route. The parenteral route includes subcutaneous, intramuscular, intravenous and sublingual administration. The topical route includes buccal and sublingual administration. The dosage at which the active ingredients are administered may vary within a wide range and will depend on various factors such as the severity of the infection, the age of patient etc., and may have to be individually adjusted. As a possible range for the amount of the compounds of the invention or a physiologically acceptable salt thereof be administered per day may be mentioned from about 10 mg to about 10 000 mg, preferentially 100-500 mg for intravenous administration and preferentially 100-1000 mg for oral administration.

Salts

The physiologically acceptable salts of the nucleosides of the invention are suitable acid addition salts, derived from non-toxic acids. Such acid addition salts include, for example, those derived from inorganic acids such as hydrochloric acid, hydroiodic acid, sulphuric acid, phosphoric acid and sulfamic acid, organic sulphonic acids such as p-toluenesulphonic acid, methanesulphonic acid, p-chlorobenzene-sulphonic acid, ethanesulfonic acid, and benzensulfonic acid and organic carboxylic acids such as maleic acid, malic acid, lactic acid, citric acid, tartaric acid, succinic acid, oxalic acid, acetic acid, isethionic acid, gluconic acid, pantothenic acid and lactobionic acid.

Experimental TestsTest I. Effect of 3'-deoxy-3'-fluorothymidine as a triphosphate on the DNA polymerase of hepatitis B virus (HBV) in cell free assay

5

Since hepatitis B virus cannot be grown in cell cultures, a cell-free assay system of the hepatitis B virus DNA polymerase has been used to investigate the effect of 3'-deoxy-3'-fluorothymidine.

3'-Deoxy-3'-fluorothymidine in cells is transformed to

10 3'-deoxy-3'-fluorothymidine-5'-triphosphate.

The HBV associated DNA polymerase activity can be measured in vitro (Kaplan et al., J. Virol., 12,995-1005, 1973). A slight modification of this method has been used to test the substance for inhibition of this DNA polymerase activity. (Nordenfelt E., Öberg, B., Helgstrand E. and Miller E. Acta path., Microbiol. Scand. Sect B, 88:169-175, 1980). With this assay the 3'-deoxy-3'-fluorothymidine-5'-triphosphate has been tested, instead of the prodrug 3'-deoxy-3'-fluorothymidine, to evaluate its potential against hepatitis B virus DNA polymerase.

20

3'-deoxy-3'-fluorothymidine-5'-triphosphate was added to the final concentrations of 0.01 μ M, 0.05 μ M, 0.1 μ M, 0.5 μ M and 1.0 μ M in the reaction mixture. The inhibition is calculated after 3 hours incubation at 37°C and based on cpm compared to control with added water. The test result is shown in Table I.

25

Table I. Inhibition of hepatitis B virus (HBV) DNA polymerase activity by 3'-deoxy-3'-fluorothymidine-5'-triphosphate

30

Concentration of 3'-deoxy-3'-fluorothymidine- 5'-triphosphate (μ M)	% inhibition
--	--------------

35

0.01	17
0.05	17
0.1	39
0.5	79
1	88

From the results shown in Table I the apparent ID_{50} -value of 3'-deoxy-3'-fluorothymidine was found to be 0.16 μM .

5 Test II. Effect of 3'-deoxy-3'-fluorothymidine as a triphosphate on the reverse transcriptase of HIV (HTLV-III/LAV) in cell free assay.

10 A cell-free assay system has been used to investigate the inhibition of 3'-deoxy-3'-fluorothymidine on reverse transcriptase of HIV (HTLV-III/LAV). The assay was performed as described by Vrang et Öberg, Antimicrob. Agents Chemother. 29,867-872 (1986). With this assay the 3'-deoxy-3'-fluoro-thymidine-5'-triphosphate has been tested, instead of the prodrug 3'-deoxy-3'-fluorothymidine to evaluate its potential against reverse transcriptase from HIV (HTLV-III/LAV). The test result is shown in Table II.

15 Table II. Inhibition of HIV (HTLV-III/LAV) reverse transcriptase by 3'-deoxy-3'-fluorothymidine-5'-triphosphate

20 Concentration of 5'-triphosphate 3'-deoxy-3'-fluorothymidine (μM)	% inhibition
0.01	12
0.05	27
0.1	38

25 From the results in Table II, the ID_{50} -value of 3'-deoxy-3'-fluoro-thymidine with regard to the activity of HIV reverse transcriptase was found to be 0.2 μM by extrapolation.

30

Test III. Effect of 3'-deoxy-3'-fluorothymidine on HIV (HTLV-III/LAV)
in H9 cells

Material and Methods; HIV Infection of H9 cells

5
H9-cells (2×10^6) were preincubated overnight with
3'-deoxy-3'-fluorothymidine at various concentrations. The cells were
then pelleted and dispersed in 2.5 ml phosphate buffered saline (PBS)
including 2 µg/ml Polybrene. After incubation for 30 min the cells were
10 pelleted and infected with HIV. After an adsorption period of 1 hour the
cells were pelleted and washed once with 2.5 ml PBS. To each culture 7
ml media including 3'-deoxy-3'-fluorothymidine at studied concentrations
was added. Samples for reverse transcriptase activity tests were taken
as indicated.

15
Assay

1.3 ml samples from the supernatant of each culture were centrifuged at
18 000 rpm in a 55-34 rotor for 1.5 hours and the virus pellet
20 resuspended in 100 µl buffer containing 50 mM Tris-HCl, pH 7.5; 35 mM
KCl; 4 mM DTT; 1 mM EDTA; 1.3 % Triton X-100. 50 µl samples were taken
to the reverse transcriptase activity tests and analyzed in a 100 µl
reaction mixture containing 75 mM Tris-HCl, pH 8.0; 60 mM KCl; 6.2 mM
MgCl₂; 6 mM DTT; 0.5 mM EDTA; 0.65 % Triton X-100; 100 µg/ml BSA; 25
25 µCi/ml ³H-dTTP (spec activity 80 Ci/mmol); 2.5 µg/ml (dT)₁₂₋₁₈; and 2.0
µg/ml (rA)_n. Incubation was for 1 hour at 37°C and the TCA-insoluble
product precipitated onto Whatman GF/A filter papers, washed and dried,
and counted in a liquid scintillation counter. The test result is shown
in Table III.

30
The amounts of reverse transcriptase molecules and their total activity
expressed in HIV-infected cell cultures is correlated to the amount of
HIV particles present. The addition of an effective antiviral agent
which inhibits the production of new HIV particles, also decreases the
35 amount of reverse transcriptase molecules and is expressed as a
decreased total activity.

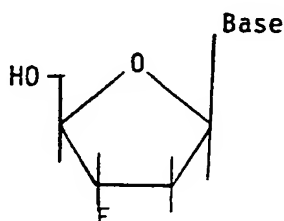
Table III. Effect of 3'-deoxy-3'-fluorothymidine on the expressed reverse transcriptase activity in HIV (HTLV-III/LAV)-infected H9 cells.

Days post-infection	Reverse transcriptase activity (cpm $\times 10^{-3}$) in the presence of indicated amounts (μM) of 3'-deoxy-3'- -fluorothymidine					
	0	0.01	0.05	0.1	0.5	1.0
4	0.9	0.5	0.3	0.2	0.3	0.3
8	19	1.3	0.3	0.2	0.3	0.2
11	17	1.9	0.4	0.5	0.5	0.5
15	11	2.7	0.6	0.4	0.3	0.4
18	27	28	0.5	0.4	0.6	0.5
22	46	52	1.6	0.2	0.1	0.1
29	16	21	3.1	0.2	0.2	0.2

In Table III is shown the effects of different concentrations of 3'-deoxy-3'-fluorothymidine on the reverse transcriptase activity of HIV (HTLV-III/LAV) during an incubation period of several weeks. The presence of 3'-deoxy-3'-fluorothymidine at 0.1 μM and higher concentrations completely prevents the enzyme activity during at least 29 days. At 0.05 μM of 3'-deoxy-3'-fluorothymidine no significant enzyme activity was detected up to 22 days and at 0.01 μM concentration, enzyme activity was not detected up to 11 days.

Claims

1. A method for therapeutic or prophylactic control and treatment of retrovirus including HIV or hepatitis B virus infections in animal and man, comprising administration to a host in need of such treatment an effective dose of a compound of the formula



15

wherein Base is thymine, cytosine, adenine or guanine, or a physiologically acceptable salt thereof.

2. A method according to claim 1. for therapeutic or prophylactic control of acquired immuno deficiency syndrome (AIDS) in animals and man.

3. A method according to claim 1 or 2 comprising administration of 3'-deoxy-3'-fluorothymidine or a physiologically acceptable salt thereof.

25

4. A method according to claims 1-3 comprising oral administration.

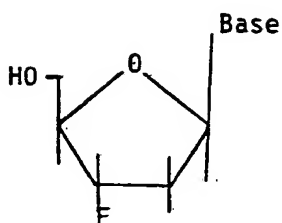
5. A method according to claims 1-3 comprising intravenous administration.

30

6. A method according to claims 1-3 comprising parenteral administration.

7. Use of a compound of the formula

5



- 10 wherein Base is thymine, cytosine, adenine or guanine, or a physiologically acceptable salt thereof, for manufacture of a medicament for therapeutic or prophylactic control or treatment of retrovirus including HIV or hepatitis B virus infections in animals and man.
- 15 8. Use of 3'-deoxy-3'-fluorothymidine, or a physiologically acceptable salt thereof, for manufacture of a medicament for therapeutic or prophylactic control or treatment of retrovirus in animals and man.
- 20 9. Use of 3'-deoxy-3'-fluorothymidine, or a physiologically acceptable salt thereof, for manufacture of a medicament for therapeutic or prophylactic control or treatment of acquired immuno deficiency syndrome (AIDS) in animals and man.
- 25 10. Use of 3'-deoxy-3'-fluorothymidine, or a physiologically acceptable salt thereof, for manufacture of a medicament for therapeutic or prophylactic control or treatment of hepatitis B virus infections in animals or man.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/SE87/00316

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) ⁶ According to International Patent Classification (IPC) or to both National Classification and IPC 4 A 61 K 31/70, C 07 H 19/04, 19/06, 19/16																	
II. FIELDS SEARCHED <div style="text-align: center; border-top: 1px solid black; border-bottom: 1px solid black;">Minimum Documentation Searched ⁷</div> <table style="width: 100%; border-collapse: collapse;"> <tr> <th style="width: 20%; border-bottom: 1px solid black;">Classification System</th> <th style="border-bottom: 1px solid black;">Classification Symbols</th> </tr> <tr> <td style="border-right: 1px solid black; padding: 5px;">IPC 2,3,4</td> <td style="padding: 5px;">A 61 K 31/70; C 07 H 19/04, /06, /067, /073, /16, /167, /173</td> </tr> <tr> <td style="border-right: 1px solid black; padding: 5px;">IPC 1</td> <td style="padding: 5px;">A 61 k 27/00 .../...</td> </tr> </table> <div style="text-align: center; border-top: 1px solid black; border-bottom: 1px solid black;">Documentation Searched other than Minimum Documentation to the extent that such Documents are included in the Fields Searched ⁸</div> <p style="text-align: center; padding: 10px 0;">SE, NO, DK, FI classes as above</p>			Classification System	Classification Symbols	IPC 2,3,4	A 61 K 31/70; C 07 H 19/04, /06, /067, /073, /16, /167, /173	IPC 1	A 61 k 27/00 .../...									
Classification System	Classification Symbols																
IPC 2,3,4	A 61 K 31/70; C 07 H 19/04, /06, /067, /073, /16, /167, /173																
IPC 1	A 61 k 27/00 .../...																
III. DOCUMENTS CONSIDERED TO BE RELEVANT ⁹ <table style="width: 100%; border-collapse: collapse;"> <tr> <th style="width: 10%; border-bottom: 1px solid black;">Category ⁹</th> <th style="border-bottom: 1px solid black;">Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²</th> <th style="width: 10%; border-bottom: 1px solid black;">Relevant to Claim No. ¹³</th> </tr> <tr> <td style="text-align: center; vertical-align: top; padding: 5px;">X</td> <td style="padding: 5px;">DD, A, 158 903 (AKADEMIE DER WISSENSCHAFTEN DER DDR) 9 February 1983 See especially page 1, first paragraph.</td> <td style="text-align: center; vertical-align: top; padding: 5px;">7</td> </tr> <tr> <td style="text-align: center; vertical-align: top; padding: 5px;">X</td> <td style="padding: 5px;">DD, A, 209 197 (AKADEMIE DER WISSENSCHAFTEN DER DDR) 25 April 1984 See especially page 1, first paragraph.</td> <td style="text-align: center; vertical-align: top; padding: 5px;">7</td> </tr> <tr> <td style="text-align: center; vertical-align: top; padding: 5px;">P,A</td> <td style="padding: 5px;">EP, A2, 0 206 497 (THE WELLCOME FOUNDATION LIMITED) 30 December 1986 See inter alia page 2, fourth paragraph, and claims 6-8. & JP, 61280500 AU, 57440/86</td> <td style="text-align: center; vertical-align: top; padding: 5px;">7</td> </tr> <tr> <td style="text-align: center; vertical-align: top; padding: 5px;">X</td> <td style="padding: 5px;">Journal für praktische Chemie, Volume 315, No. 5, issued 1973 (Leipzig), G. Kowollik et al, "Ein neuer Zugang zur (2,3-Didesoxy-3-fluor-A-D-ribofuranosyl)-pyrimidinen", .../...</td> <td style="text-align: center; vertical-align: top; padding: 5px;">7-10</td> </tr> </table> <div style="font-size: small; padding: 5px;"> <div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <p>⁹ Special categories of cited documents: ¹⁰</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="width: 45%;"> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"a" document member of the same patent family</p> </div> </div> </div>			Category ⁹	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³	X	DD, A, 158 903 (AKADEMIE DER WISSENSCHAFTEN DER DDR) 9 February 1983 See especially page 1, first paragraph.	7	X	DD, A, 209 197 (AKADEMIE DER WISSENSCHAFTEN DER DDR) 25 April 1984 See especially page 1, first paragraph.	7	P,A	EP, A2, 0 206 497 (THE WELLCOME FOUNDATION LIMITED) 30 December 1986 See inter alia page 2, fourth paragraph, and claims 6-8. & JP, 61280500 AU, 57440/86	7	X	Journal für praktische Chemie, Volume 315, No. 5, issued 1973 (Leipzig), G. Kowollik et al, "Ein neuer Zugang zur (2,3-Didesoxy-3-fluor- A-D -ribofuranosyl)-pyrimidinen", .../...	7-10
Category ⁹	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³															
X	DD, A, 158 903 (AKADEMIE DER WISSENSCHAFTEN DER DDR) 9 February 1983 See especially page 1, first paragraph.	7															
X	DD, A, 209 197 (AKADEMIE DER WISSENSCHAFTEN DER DDR) 25 April 1984 See especially page 1, first paragraph.	7															
P,A	EP, A2, 0 206 497 (THE WELLCOME FOUNDATION LIMITED) 30 December 1986 See inter alia page 2, fourth paragraph, and claims 6-8. & JP, 61280500 AU, 57440/86	7															
X	Journal für praktische Chemie, Volume 315, No. 5, issued 1973 (Leipzig), G. Kowollik et al, "Ein neuer Zugang zur (2,3-Didesoxy-3-fluor- A-D -ribofuranosyl)-pyrimidinen", .../...	7-10															
IV. CERTIFICATION <table style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 50%; border-bottom: 1px solid black; padding: 5px;"> Date of the Actual Completion of the International Search 1987-09-18 </td> <td style="width: 50%; border-bottom: 1px solid black; padding: 5px;"> Date of Mailing of this International Search Report <div style="text-align: center; font-weight: bold;">24. 09. 87</div> </td> </tr> <tr> <td style="border-bottom: 1px solid black; padding: 5px;"> International Searching Authority Swedish Patent Office </td> <td style="border-bottom: 1px solid black; padding: 5px;"> Signature of Authorized Officer <div style="text-align: center;"> Martin Hjalmdahl </div> </td> </tr> </table>			Date of the Actual Completion of the International Search 1987-09-18	Date of Mailing of this International Search Report <div style="text-align: center; font-weight: bold;">24. 09. 87</div>	International Searching Authority Swedish Patent Office	Signature of Authorized Officer <div style="text-align: center;"> Martin Hjalmdahl </div>											
Date of the Actual Completion of the International Search 1987-09-18	Date of Mailing of this International Search Report <div style="text-align: center; font-weight: bold;">24. 09. 87</div>																
International Searching Authority Swedish Patent Office	Signature of Authorized Officer <div style="text-align: center;"> Martin Hjalmdahl </div>																

L.E.

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

II Fields Searched (cont).

US C1 424:180;
514:23, 25, 42, 43, 45, 46, 49

V. ☒ OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE ¹

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. ☒ Claim numbers 1-6 because they relate to subject matter not required to be searched by this Authority, namely:

Methods for treatment of the human or animal body by therapy (PCT, Rule 39 (iv)).

2. ☐ Claim numbers _____, because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claim numbers _____, because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. ☐ OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING ²

This International Searching Authority found multiple inventions in this international application as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.
2. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:
3. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:
4. ☐ As all searchable claims could be searched without effort justifying an additional fee, the international searching authority did not invite payment of any additional fee.

Remark on Protest

- ☐ The additional search fees were accompanied by applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)		
Category *	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No
	see pages 895-900, especially p. 895, second paragraph.	
X	Chemical Abstracts, Vol. 84 (1976), abstract No. 25824 u, Vopr. Virusol. 1975, (5), 625-6 (Russ).	7-10
A	Chemical Abstracts, Vol. 102 (1985), abstract No. 39565 n, J. Cell. Physiol. 1984, 121 (2), 402-8 (Eng), see especially the last three lines of the abstract.	7
X	Progress in Antimicrobial and Anticancer Chemotherapy: Proceedings of the 6th International Congress of Chemotherapy, Volume II, published 1970, by University Park Press (Baltimore), see pages 394-397, especially p. 397, lines 11-12 after the table.	7-10

**This Page is Inserted by IFW Indexing and Scanning
Operations and is not part of the Official Record**

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- ☐ **BLACK BORDERS**
- ☐ **IMAGE CUT OFF AT TOP, BOTTOM OR SIDES**
- ☐ **FADED TEXT OR DRAWING**
- ☐ **BLURRED OR ILLEGIBLE TEXT OR DRAWING**
- ☐ **SKEWED/SLANTED IMAGES**
- ☐ **COLOR OR BLACK AND WHITE PHOTOGRAPHS**
- ☐ **GRAY SCALE DOCUMENTS**
- ☐ **LINES OR MARKS ON ORIGINAL DOCUMENT**
- ☐ **REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY**
- ☐ **OTHER:** _____

IMAGES ARE BEST AVAILABLE COPY.

As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.